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Health Effects Assessment for Aluminum

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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HEALTH EFFECTS ASSESSMENT FOR ALUMINUM

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with aluminum and compounds. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1984. Drinking Water Criteria Document for Aluminum. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. External Review Draft.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

In a short-term balance study using healthy humans, 125 mg aluminum/day added to the diet was homeostatically controlled with no adverse effects being noted (Greger and Baier, 1983a). Up to 200 mg/day in the diets of humans may be associated with reduced phosphorus absorption from the gastrointestinal tract, but not with impaired body function (Campbell et al., 1957; Greger and Baier, 1983b).

No RfD values were calculated for aluminum. A CS of 10 for aluminum was based on pulmonary and thoracic effects leading to death in a chronic study in rats exposed by inhalation to aluminum oxide (Klosterkotter, 1960).

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LIST OF ABBREVIATIONS

ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
ATP	Adenosine triphosphate
CAS	Chemical Abstract Service
CS	Composite score
DMSO	Dimethyl sulfoxide
FEL	Frank effect level
HA	Health advisory
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical and chemical properties of aluminum and some of its compounds are listed in Table 1-1. Aluminum (CAS no. 7429-90-5) is a metallic element with an oxidation state of +3 except under extreme conditions when oxidation states of +2 and +1 have been found (Rollinson, 1978). Aluminum does not exist naturally in the elemental form (U.S. EPA, 1980b), but is found in ~300 minerals (e.g., silicates, feldspars, micas and clays) (U.S. EPA, 1984a).

Aluminum is soluble in acids and bases, particularly nitric acid, hot acetic acid, sulfuric and hydrochloric acids and alkalis. In the environment, it may exist as stable aluminum salts or as organo-aluminum compounds (Driscoll, 1985; U.S. EPA, 1984a). The half-lives of aluminum and compounds in air, water and soil could not be located in the available literature. In the atmosphere, aluminum is expected to be present mainly in particulate form as a result of industrial emissions, fossil fuel burning and natural emissions including those from volcanic sources. The ratio of aluminum emissions from anthropogenic sources to natural sources is 0.15 (Fishbein, 1981). Monitoring data indicate that aluminum is removed from the atmosphere by particulate settling and washout in precipitation (Landsberger et al., 1983; Davidson et al., 1985; Wiersema et al., 1984). Particles emitted from anthropogenic sources tend to be smaller in size and transport over longer distances than those emitted from natural sources (Fishbein, 1981). The level of Al found in natural waters varies geographically. In waters where pH is <5, as with industrial wastes, mine runoff, acidic spring waters, mires and volcanic areas, the aluminum level can exceed 100 mg/ℓ. At pH levels >5.5, Al^{+3} is nearly insoluble.

TABLE 1-1

Physical and Chemical Properties of Aluminum and Aluminum Compounds[a]

Compound	CAS Number	Description	Boiling Point (°C)	Melting Point (°C)	Vapor Pressure	Water Solubility	Molecular Weight
Aluminum	7429-90-5	silvery white crystalline solid	2467	660	1 mm Hg (1284°C)	insoluble nil (25°C)	26.9815
Aluminum acetate (tri-)	139-12-8	white solid	NA	decomposes	NA	very slightly	204.12
Aluminum acetylacetonate	13963-57-0	colorless solid	314	193	NA	insoluble	324.31
Aluminum acetylsalicylate	147-31-9	white to off-white powder or granules	NA	decomposes	NA	nearly insoluble	402.30
Aluminum barium oxide	12004-04-5	solid	NA	NA	NA	NA	255.29
Aluminum benzoate	555-32-8	white crystalline powder	NA	NA	NA	very slightly soluble	390.33
Aluminum borate	11121-16-7	white granular powder	NA	1050	NA	nearly insoluble	273.56
Aluminum boride	12041-50-8	copper-red solid	NA	975 decomposes	NA	NA	48.60
Aluminum borohydride	16962-07-5	volatile pyrophoric liquid	44.5	-64.5	NA	decomposes	71.53
Aluminum bromide (anhydrous)	7727-15-3	white to yellow solid	265	97.5	NA	soluble with violence	266.72
Aluminum bromide (hexahydrate)	7784-11-4	white to yellow solid	decomposes	93	NA	soluble	374.80
Aluminum sec-butoxide	2269-22-9	white to yellow crystals	180 (0.4 mm Hg)	88-101.5	NA	decomposes	246.33
Aluminum tert-butoxide	555-91-2	powder	NA	sublimes (180°C)	NA	NA	246.33
Aluminum carbide	1299-86-1	yellow crystals or powder	NA	2100	NA	decomposes	143.91
Aluminum carbonate, basic	1339-92-0	white solid	NA	NA	NA	insoluble	variable

TABLE 1-1 (cont.)

Compound	CAS Number	Description	Boiling Point (°C)	Melting Point (°C)	Vapor Pressure	Water Solubility	Molecular Weight
Aluminum chlor-hydroxy allantoinate	1317-25-5	white to off-white powder	NA	NA	NA	insoluble	NA
Aluminum chromate	54991-58-1	yellow amorphous salt	NA	NA	NA	NA	variable
Aluminum dihy-droxy allantoinate	5579-81-7	white to off-white powder	NA	NA	NA	insoluble	NA
Aluminum 2-ethyl-hexanoate	6028-57-5	solid	NA	NA	NA	NA	456.50
Aluminum formate (normal)	7360-53-4	white crystalline powder	NA	NA	NA	slightly soluble (cold) 25% soluble (boiling)	162.03
Aluminum formo-acetate	61827-57-4	white powder	NA	NA	NA	soluble	148.05
Aluminum iodide (anhydrous)	7784-23-8	brownish-black pieces commercially	382-385	191	NA	soluble	407.73
Aluminum iso-propoxide	555-31-7	white solid	138-148 (10 mm Hg)	128-133	NA	decomposes	204.25
Aluminum magn-esium carbonate hydroxide	14492-59-2	solid	NA	NA	NA	NA	130.31
Aluminum mono-stearate	7047-84-9	fine white to yellowish-white powder	NA	155	NA	insoluble	344.5
Aluminum naph-thenate	NA	yellow substance, rubbery consistency	NA	NA	NA	NA	NA
Aluminum nitride	24304-00-5	bluish-white crystals	200 sublimes	>2200 (in N_2)	NA	decomposes	40.99
Aluminum octanoate	6028-57-5	solid	NA	NA	NA	NA	474.4
Aluminum oleate	688-37-9	yellowish-white viscous mass	NA	NA	NA	insoluble	871.36
Aluminum palmitate	555-35-1	white powder	NA	200	NA	insoluble	318.41

TABLE 1-1 (cont.)

Compound	CAS Number	Description	Boiling Point (°C)	Melting Point (°C)	Vapor Pressure	Water Solubility	Molecular Weight
Aluminum phenol-sulfonate	1300-35-2	reddish-white powder	NA	NA	NA	soluble	546.49
Aluminum meta-phosphate	13776-88-0	white powder	NA	1537	NA	insoluble	263.90
Aluminum phosphide	20859-73-8	dark gray to dark yellow crystals	NA	>1000	NA	decomposes	57.96
Aluminum resinate	61789-65-9	brown solid	NA	NA	NA	insoluble	variable
Aluminum sulfate	7784-31-8	white powder[b]	NA	NA	NA	2.78×10^5 (25°C)[c]	342.14[b]
Aluminum tristea-rate	637-12-7	white powder	NA	115	NA	insoluble	877.4
Calcium aluminate	12042-78-3	white crystals or powder	NA	decomposes (1535°C)	NA	insoluble	270.20
Diethylaluminum ethoxide	1586-92-1	NA	NA	NA	NA	NA	130.16
Diethylaluminum fluoride	367-44-0	colorless liquid	90-100 (1-2 mm Hg)	NA	NA	NA	104.11
Diethylaluminum hydride	871-27-2	colorless pyrophoric liquid	55-56 (10^{-3} to 10^{-4} mm Hg)	NA	NA	decomposes	86.11
Diethylaluminum iodide	2040-00-8	colorless liquid	262	NA	NA	NA	212.00
Diisobutylaluminum chloride	1779-25-5	colorless liquid	152 (10 mm Hg)	-39.5	NA	decomposes	176.66
Diisobutylaluminum hydride	1191-15-7	colorless pyrophoric liquid	105 (0.2 mm Hg)	-80	NA	decomposes	142.22
Dimethylaluminum chloride	1184-58-3	colorless liquid	126-127	-21 to -45	NA	NA	92.50
Ethylaluminum dichloride	563-43-9	clear, yellow pyrophoric liquid	194 (extrapolated)	32	NA	decomposes	126.94

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TABLE 1-1 (cont.)

Compound	CAS Number	Description	Boiling Point (°C)	Melting Point (°C)	Vapor Pressure	Water Solubility	Molecular Weight
Ethylaluminum sesquichloride	12075 68-2	clear, yellow pyrophoric	204	-50	NA	decomposes	247.50
Isobutylaluminum dichloride	1888-87-5	liquid	118 (10 mm Hg)	-29.8	NA	NA	155.00
Isobutylaluminum sesquichloride	NA	NA	NA	NA	NA	NA	331.66
Isoprenylaluminum	NA	NA	NA	NA	NA	NA	NA
Lithium aluminate	12003-67-7	white powder	NA	1900-2000	NA	insoluble	65.92
Lithium aluminum hydride	16853-85-3	white crystalline solid	NA	decomposes (125°C)	NA	decomposes	37.95
Magnesium aluminum silicate	1327-43-1	solid	NA	NA	NA	NA	variable
Methylaluminum sesquichloride	12541-85-7	colorless liquid	143.7	22.8	NA	decomposes	205.42
Sodium aluminum diethyl dihydride	NA	25% solution in aromatic	NA	60	NA	NA	NA
Tri-n-decylaluminum	1726-66-5	NA	NA	NA	NA	NA	450.82
Trimethylaluminum	75-24-1	colorless pyrophoric liquid	126	15.4	NA	NA	72.09
Tri-2-methylpentyl-aluminum	NA	NA	NA	NA	NA	NA	282.49
Tripropylaluminum	102-67-0	colorless pyrophoric liquid	110	-84 (13 mm Hg)	NA	NA	156.25

[a]Source: U.S. EPA, 1984a (unless indicated otherwise)

[b]Weast, 1985

[c]Darragh, 1978

NA - Not available

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Substances dissolved in the water also affect aluminum water solubility. Complexing ligands such as fluoride, phosphate and sulfate, and chelating agents such as ethylenediamine tetracetic acid, nitrilotriacetic acid and sodium tripolyphosphate will also increase the water solubility of aluminum. The aluminum ion also complexes with hydroxide under aqueous conditions.

Since aluminum is more soluble in water at an acidic pH, it is likely that it will accumulate in aquatic organisms and vegetation under these conditions. Evidence of photodegradation or oxidation of aluminum in water is not available (U.S. EPA, 1984a). Strong bonding with humic substances in sediments by aluminum is expected (Raspor et al., 1984).

The fate of aluminum in soil will vary depending upon soil characteristics, such as soil type, pH and ion species present (Driscoll, 1985). Aluminum can be immobilized by strong binding with humic substances (Raspor et al., 1984; Driscoll, 1985) and can be mobilized by complexing with HCO_3^- organic and other acidic counteranions (Driscoll, 1985).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Greger and Baier (1983a) conducted a balance study with eight healthy men. Four of the subjects were given a control diet containing 4.6 mg aluminum/day for 20 days, while the other four subjects received a test diet of 125 mg aluminum/day as aluminum lactate. The diets were exchanged for an additional 20 days with each subject acting as his own control. Fecal, urine and serum aluminum determinations indicated that some absorption with rapid elimination occurred at 125 mg/day. Other studies with different aluminum compounds (e.g., aluminum carbonate, aluminum hydroxide) showed that doses $\geq$1000 mg aluminum/day resulted in significant gastrointestinal absorption and retention of aluminum (Recker et al., 1977; Gorsky et al., 1979; Clarkson et al., 1972; Cam et al., 1976). Although the data indicate that homeostatic regulation of aluminum is effective at doses of $\leq$125 mg aluminum/day, studies that investigated the absorption of oral doses of aluminum between 125 and 1000 mg/day are not available (U.S. EPA, 1984a). Gastrointestinal absorption of aluminum varies not only with the concentration of aluminum but also with type of aluminum compound and pH (Savory et al., 1983).

Krigman et al. (1985) concluded that aluminum is absorbed from the human gastrointestinal tract regardless of the form in which it occurs. They indicated that the proportion of ingested aluminum absorbed is small and estimate that ~35 mg/day is ingested. In a review of the pathogenesis of the nervous disorder, dialysis encephalopathy, Arieff (1985) stated that "significant absorption of oral aluminum can occur in patients with chronic renal failure," implying that absorption may be enhanced in these patients and that they may be a group with increased risk to the toxicity of aluminum.

2.2. INHALATION

Studies with humans have shown that aluminum accumulates in the lungs with age (Tipton and Shafer, 1964; Alfrey, 1980) and that aluminum levels in the lungs were relatively high compared with other tissues, including the trachea, gastrointestinal tract and visceral organs (Teraoka, 1981). Although this information suggests that pulmonary absorption of aluminum dusts may have occurred, this cannot be concluded definitely because serum aluminum levels and other pertinent endpoints were not assessed. Particle size and solubility of aluminum particulate and compounds may determine their fate in the lungs (U.S. EPA, 1984a).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Aluminum interacts with phosphorus in the gastrointestinal tract to form insoluble aluminum phosphate, which is readily excreted (U.S. EPA, 1984a). Prolonged aluminum intake from antacids (aluminum hydroxide) can lead to phosphorus depletion with hypercalciuria, bone resorption and osteomalacia in humans.

As discussed in Section 2.1., humans treated with aluminum added to the diet at 125 mg/day (1.8 mg/kg/day) homestatically eliminate the absorbed excess without evidence of ill effects.

It appears that dietary intake at levels up to ~200 mg aluminum/day, although associated with decreased gastrointestinal uptake of phosphate, is not sufficient to interfere with bodily function (Campbell et al., 1957; Greger and Baier, 1983b). Intake of aluminum compounds in the form of antacids in amounts of $\geq$1 g aluminum/day may cause significant interaction with phosphorus in healthy individuals (Insogna et al., 1980; U.S. EPA, 1984a).

Persons with severe reduction of renal function are commonly given aluminum hydroxide orally in large amounts (~3 g aluminum/day) to prevent hyperphosphatemia (U.S. EPA, 1984a). This large aluminum load may lead to increased aluminum levels in the bone and possibly the brain, which can result in osteomalacia and dialysis encephalopathy. An increased risk for encephalopathy has been determined when serum levels of aluminum are >100 µg/mℓ as compared with normal levels of ~5 µg/ℓ (U.S. EPA, 1984a). High brain aluminum levels have also been associated with encephalopathy in the elderly and in Alzheimer's patients, but it has not been established if aluminum acts as a direct causative agent (U.S. EPA, 1984a).

Aluminum chloride was administered orally (apparently by gavage in water) to unspecified numbers of male rats and male guinea pigs at doses of 0, 6, 17 and 50 mg aluminum/kg/day and to male rabbits at doses of 0, 3, 9 and 27 mg aluminum/kg/day for 20-30 days (Krasovskii et al., 1979). Assays apparently conducted 3 hours after cessation of treatment showed decreased activity of serum alkaline phosphatase at ≥17 mg/kg/day in the rats and guinea pigs, and ≥9 mg/kg/day in the rabbits. Serum levels of ATP, ADP and AMP were significantly decreased in the rats and guinea pigs at ≥17 mg/kg and in the rabbits at 27 mg/kg. Rats were also similarly exposed to 0.0025, 0.25 or 2.5 mg aluminum/kg/day (as aluminum chloride) for 6-12 months (Krasovskii et al., 1979). Effects included decreased serum alkaline phosphatase and depressed motor reflexes at 2.5 mg/kg; alkaline phosphatase was also decreased at 0.25 mg/kg, but only during the first month of exposure. Treatment-related effects on blood erythrocytes B-lipoproteins or unspecified transaminase activity were not observed. Additional information regarding the design or results of the Krasovskii et al. (1979) experiments was not reported.

Gross and histological examinations of the liver, lungs, spleen, kidneys, brain, heart and testes of groups of seven male Sprague-Dawley rats exposed to 0, 5, 50 or 500 mg aluminum/ℓ (as aluminum chloride) in the drinking water for 30, 60 or 90 days were unremarkable (Dixon et al., 1979).

Groups of eight male Fischer or eight female Sprague-Dawley rats were subjected to behavioral tests that assessed coordination, locomotor activity and learning at different points throughout a 12-week period in which 0.2% aluminum (as aluminum chloride) was administered in the diet (Commissaris et al., 1982). Significantly depressed locomotor activity occurred in the

females; the males only showed a trend in this effect. If it is assumed that rats consume the equivalent of 5% of their weight in food per day, the daily dosage was 100 mg aluminum/kg/day.

Dietary administration of 0.1% aluminum (as aluminum chloride) for 11 months depressed locomotor activity and learning (acquisition of avoidance behavior) in Sprague-Dawley rats (Commissaris et al., 1982). This exposure corresponds to 50 mg/kg/day if it assumed that rats consume the equivalent of 5% of their weight in food per day.

3.1.2. Inhalation. Gross et al. (1973) exposed groups of 14-30 guinea pigs, rats and hamsters to five metallic aluminum powders (pyro, atomized and flaked) at air concentrations of 15, 30, 50 or 100 mg/m^3, 6 hours/day, 5 days/week for 6 months. Alveolar proteinosis occurred in all three species after 2 months of exposure but other adverse pulmonary effects, including fibrosis, did not develop.

Groups of 35 Fischer rats/sex and 35 Hartley guinea pigs/sex were exposed to 0.25, 2.5 or 25 mg/m^3 aluminum chlorohydrate, 6 hours/day, 5 days/week for 6 and 12 months (Cavender et al., 1978). After 6 months, alveolar macrophages were increased at all three exposure levels; decreased body weight, increased lung-to-body weight ratios and multifocal granulomatous pneumonia also occurred at 25 mg/m^3. Granulomas occurred in the lungs of 2.5 mg/m^3 animals (both species) after 12 months of exposure. It should be noted that the actual structure of aluminum chlorohydrate is not known, but is considered to be a complex of basic aluminum chloride and propylene glycol.

Information regarding effects of exposure to soluble salts of aluminum (e.g., chloride and sulfate) could not be located. It appears, however,

that for soluble salts of aluminum, effects may be acute in nature and associated with the corresponding acid formed by hydrolysis of the aluminum compound. Reflecting this, the TLV for soluble aluminum salts of 2 mg/m³ is based on the TLV for hydrochloric acid assuming 1 mol of aluminum chloride yields 3 mol of HCl on hydrolysis and assuming similar toxic potencies for the acids formed by hydrolysis of different aluminum salts.

3.2. CHRONIC

3.2.1. Oral. Aluminum chloride was administered to groups of 10 mice in drinking water at an average dose of 0 or 19.3 mg aluminum/kg/day in a 3-generation study (Ondreicka et al., 1966). The parental generation was treated for 180-390 days and unspecified numbers of weanlings were similarly treated from 4 weeks of age. Decreased body weight in the second and third generations was the only effect of treatment. Erythrocyte counts, hemoglobin levels and histology of the liver, spleen and kidneys in mice from the first and third generation were similar to controls. The significance of the decreased weight gain is difficult to assess, however, since food consumption was not reported; decreased food intake was observed with aluminum exposure in other studies included in the same report.

Schroeder and Mitchener (1975a) administered 5 ppm aluminum (as aluminum potassium sulfate) in the drinking water of 52 Long-Evans rats/sex for life. Exposed rats did not differ from controls with respect to body weight, survival, selected serum chemistries (glucose, cholesterol, uric acid) selected urinalysis parameters (protein, glucose, pH) or tissue histology (heart, lung, kidney, liver or spleen).

Groups of 54 weanling Swiss mice/sex were exposed to 0 or 5 mg aluminum/L (as aluminum potassium sulfate) in the drinking water for life (Schroeder and Mitchener, 1975b). If it is assumed that mice consume water equivalent to 17% of their weight per day, the dosage is 0.85 mg/kg day.

Treatment had no effect on body weight, survival, edema, blanching of the incisor teeth, or tissues as indicated by gross and limited histological ("some sections" were made of the heart, lung, liver, kidney and spleen) examinations.

3.2.2. Inhalation. Pulmonary fibrosis has been associated with occupational exposure to aluminum powder (metallic aluminum covered with a complex oxide/hydroxide coating) or alumina (Al_2O_3) dust in a number of reports (U.S. EPA, 1984a); however, U.S. EPA (1984a) demonstrated that these reports are inconclusive because confounding factors such as concurrent exposure to other chemicals (e.g., alloying agents, chemicals used in the production of fireworks, inks and paints or silica), cigarette smoking (which contributed directly to the lung burden of aluminum and silicon) or previous workplace exposures were not always evaluated. ACGIH (1986) and U.S. EPA (1984a) report that there is no evidence of fibrogenic activity of aluminum or alumina at exposure levels currently recommended by the ACGIH (10 mg/m³ for dust, 5 mg/m³ for powder) and suggest that they be classified as inert (nuisance) particulates. Past exposures associated with fibrotic lung changes occurred at extremely high concentrations in poorly or uncontrolled occupational environments; insufficient monitoring data preclude estimation of typical TWA concentrations of aluminum.

Aluminum powders have been administered to humans in known exposures in the treatment of silicosis. Stokinger (1981) reviewed data in which >42 million aluminum treatments (~150,000 man-years) had been given over a 27-year period ending in 1971. Inhalation of ~350 mg/m³ of respirable alumina powder for 10 minutes/day did not result in lung damage or other ill effects; this exposure reportedly is equivalent to an 8-hour TWA concentration of 7 mg/m³ (U.S. EPA, 1984a). The data from this study were used as the basis for the TLV (Stokinger, 1981; ACGIH, 1986).

Exposure to 2.18 mg/m³ aluminum fibers, 6 hours/day, 5 days/week for up to 86 weeks produced slight increases in alveolar macrophages and some irritation of the nasal passages in a group of 50 Alderly Park rats (Pigott et al., 1981). Lung edema, pneumonia and pleurisy were observed in 107/145 rats that died from exposure to 33 g/m³ aluminum oxide (Al_2O_3), 5 hours/day for up to 285/402 days (Klosterkotter, 1960).

The responses observed in the above animal studies are typically elicited by nuisance particulate exposure.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Groups of 31 male Sprague-Dawley rats were administered 0, 5, 50 or 500 mg aluminum/L (as aluminum chloride) in the drinking water (Dixon et al., 1979). Seven rats from each group were sacrificed after 30, 60 and 90 days for plasma lutenizing hormone and follicle-stimulating hormone determinations, and histological examination of the testes. The remaining 10 males from each group were mated after 90 days of treatment; a different female was paired with each male every 7 days for a total of 70 days. Treatment-related effects on reproductive capacity as indicated by the above evaluation were not observed. Endpoints in the reproduction study included pregnancy rate, implantation sites, corpora lutea, resorption sites and live and dead implants.

Decreased spermatozoa counts and sperm motility reportedly occurred in rats that were exposed to 2.5 mg aluminum/kg/day (as aluminum chloride) by gavage but not at lower doses (0.0025 or 0.25 mg/kg/day) for 6 months (Krasovskii et al., 1979). Histological and histochemical alterations in the testes were also observed at the 2.5 mg/kg/day dose. As indicated in Section 3.1.1., aspects of this report are inadequate.

Anderson et al. (1985) exposed sperm-positive Holtzman rats to plain tap water (four rats) or to a Maalox TC-tap water mixture at a 1:4 ratio (six rats) beginning on day 2 of gestation until weaning to test the effects of high ingested levels of aluminum on reproductive performance. Water intake was not measured and aluminum intake was not estimated. At parturition, one control and one treated litter were cross-fostered to evaluate the effects of high levels of ingested aluminum on maternal care. One aluminum-exposed litter was aborted, but all control dams delivered normally. Body weights were reduced ($p<0.05$, Neuman-Kenls test) in aluminum-exposed rats at birth and at time points up to 70 days postpartum ($p<0.01$) in litters maintained with dams exposed until weaning. Body weights of pups from treated dams recovered if the pups were cross-fostered by an untreated dam.

3.3.2. Inhalation. Pertinent data could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

As indicated in Section 2.1., aluminum interacts with phosphorus in the gastrointestinal tract to form insoluble aluminum phosphate, which is readily excreted (U.S. EPA, 1984a). Fluoride has also been shown to react with aluminum in the gastrointestinal tract (U.S. EPA, 1984a).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data could not be located in the available literature.

4.1.2. Inhalation. Occupational exposure to aluminum has not been associated with pulmonary or systemic neoplastic alterations in humans (U.S. EPA, 1984a; ACGIH, 1986; Stokinger, 1981).

4.2. BIOASSAYS

4.2.1. Oral. Schroeder and Mitchener (1975a) administered drinking water containing 5 mg/ℓ aluminum (as aluminum potassium sulfate) to groups of 52 Long-Evans weanling rats/sex for life. Effects on body weight or longevity were not observed, but 13 males and 14 females died at age 20 months from nontreatment-related pneumonia. Gross and limited (heart, lung, kidney, liver, spleen, tumors) histological examinations were conducted.

The incidence of total gross tumors (all sites) was significantly ($p<0.005$) increased in treated males (13/25 vs. 4/26). Incidences of specific types of tumors were not specified, but incidences of tumors considered malignant (multiple tumors in the same animal) were 6/25 in the treated and 2/26 in the controls. The authors considered aluminum to be innocuous. Schroeder and Mitchener (1975b) also administered aluminum potassium sulfate in the drinking water (5 mg aluminum/ℓ) of groups of 54 Swiss mice/sex for life. Treatment had no effect on body weights or survival. Gross pathological and limited histological examinations revealed an increased incidence of lymphoma leukemia in the treated females (10/41 vs. 3/47, $p<0.025$); however, the authors did not consider the compound to be tumorigenic.

4.2.2. Inhalation. Groups of 35 rats and guinea pigs/sex were exposed by inhalation to 0.25, 2.5 or 25 mg/m³ of aluminum chlorohydrate 6 hours/day, 5 days/week for 6-12 months (Cavender et al., 1978). Lung granulomas occurred in both species following exposure to 25 mg/m³ for 6 months and 2.5 mg/m³ for 12 months.

Granulomatous nodules were also observed in male hamsters that were exposed 6 hours/day, 5 days/week for 20 or 30 exposures to average aluminum chlorohydrate concentrations of 52 mg/m³ (Drew et al., 1974). These alterations persisted up to 6 weeks postexposure but only minor changes (a few foci of macrophages and heterophils) occurred after 10 exposures. Groups of four exposed and four control hamsters were sacrificed after 10, 20 and 30 exposures and 2, 4 and 6 weeks postexposure). The granulomatous foci consistently developed at the bifurcation of the bronchioloalveolar ducts, a probable site of particulate deposition.

4.3. OTHER RELEVANT DATA

Administration of aluminum or aluminum compound (aluminum hydroxide, oxide or phosphate) by different routes (intratracheal, intraperitoneal, intravenous, subcutaneous implant) in rats, guinea pigs and hamsters did not elicit treatment-related tumor formation (O'Gara and Brown, 1967; Shubich and Hartwell, 1969; Wagner et al., 1973; Stenback et al., 1976; Turk and Parker, 1977).

Elemental aluminum dissolved in DMSO was not mutagenic in Salmonella typhimurium strains TA98, TA1535 and TA1538 (Milvy and Kay, 1978). Aluminum chloride ($AlCl_3$) did not produce effects in a DNA damage/repair assay with Bacillus subtilis strains M45 (rec^-) and H17 (rec^+) (Nishioka, 1975), but did produce chromatid breaks and gaps in mouse bone marrow cells in vitro (Manna and Das, 1972).

4.4. WEIGHT OF EVIDENCE

Aluminum potassium sulfate was administered in the drinking water of rats (Schroeder and Mitchener, 1975a) and mice (Schroeder and Mitchener, 1975b) at a concentration of 5 mg aluminum/ℓ for life. The incidence of total tumors was significantly increased in the male rats but incidences or characterization of specific types of tumors were not reported. The incidence of lymphoma leukemia was significantly increased in the female mice. Granulomas developed in the lungs of rats and guinea pigs that inhaled 2.5 mg/m³ aluminum chlorohydrate, 6 hours/day, 5 days/week for 12 months or 25 mg/m³ for 6 months (Cavender et al., 1978). Exposure to 52 mg/m³ aluminum chlorohydrate (20-30 exposures, 6 hours/day, 5 days/week) produced a similar response in hamsters (Drew et al., 1974). These responses cannot definately be attributed solely to aluminum, however, because the actual structure of aluminum chlorohydrate is not known (see Section 3.1.2.). The available data are inadequate for evaluating the carcinogenicity of aluminum. Aluminum is, therefore, most appropriately categorized in IARC Group 3 and CAG Group C according to the guidelines for evaluating the weight of evidence of human carcinogenic potential (U.S. EPA, 1986).

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1986) currently recommends 8-hour TWA TLVs of 10, 5, 5, 2 and 2 mg aluminum/m^3 for occupational exposure to aluminum metal dusts, pyro powders, welding fumes, soluble salts and alkyls, respectively.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). As discussed in Sections 3.1.1. and 3.1.2., the mechanism of aluminum toxicity appears to be indirect, resulting from the interaction of aluminum and phosphate. Excessive exposure to aluminum is associated with phosphate depletion, resulting in bone resorption, osteomalacia and hypercalciuria. Results of the Greger and Baier (1983a,b) study indicate that absorption of aluminum occurs in healthy humans treated with 125 mg aluminum/day without retention in the body and that effects on phosphorus absorption in the gastrointestinal tract at this dose are very small and physiologically insignificant. Although homeostatic control of aluminum appears to be effective at 125 mg aluminum/day, the minimal effects on phosphorus absorption indicate that this intake may represent a NOAEL. In humans, ingestion of 1 g aluminum (14.3 mg/kg/day) is associated with significant interaction with phosphorus in healthy individuals (Insogna et al., 1980). In subchronic animal tests, 2.5 mg aluminum/kg/day has been associated with decreased serum alkaline phosphatase and depressed motor reflexes in rats (Krasovskii et al., 1979) and 100 mg/kg/day with depressed locomotor activity in rats (Commissaris et al., 1982).

6.1.2. Inhalation (RfD_{SI}). Subchronic data regarding the toxicity of aluminum, soluble salts of aluminum, and aluminum alkyls are insufficient for derivation of an RfD_{SI} for these compounds.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_O). The available data were deemed insufficient for RfD_O calculation.

Long-term intake of aluminum compounds (e.g., aluminum hydroxide in antacids) in amounts of ~1 g aluminum/day or more may cause phosphate depletion, which can eventually lead to osteomalacia (U.S. EPA, 1980b).

Smaller amounts of aluminum will cause decreased uptake of phosphate that is not severe enough to elicit adverse effects. Higher dosages (~3 g aluminum/day), administered to persons with severe reduction of renal function to prevent hyperphosphatemia, can lead to accumulation of aluminum in the brain and dialysis encepalopathy. A CS can be calculated for aluminum by regarding the 1 g aluminum/day intake as the MED for phosphorus depletion. The RV_d associated with this MED is 1. If phosphate depletion potentially resulting in adverse physiological effects is assigned an RV_e of 7, the CS is 7.

6.2.2. Inhalation (RfD_I). As discussed in Section 3.1.2., there is no evidence of fibrogenic activity or other nonreversible pulmonary effects of aluminum powders or alumina dusts at the TLVs (5 mg/m³ for pyro powder, 10 mg/m³ for dust) (ACGIH, 1986). TWA concentrations reflect possible human NOAELs but cannnot be used to calculate an RfD_I for aluminum. It should be noted that local pulmonary effects of aluminum are presumed to be independent of homeostatic regulation.

Granulomatous pneumonia occurred in rats and guinea pigs that were exposed to 0.25, 2.5 or 25 mg/m³ aluminum chlorohydrate by inhalation, 6 hours/day, 5 days/week for 6 months (Cavender et al., 1978); granulomas developed after 12 months exposure to 25 mg/m³. These data are inappropriate for RfD_{SI} calculation because the effects have not been observed in humans at comparable or higher exposures and, furthermore, because the effects cannot definitely be attributed to aluminum.

Although ACGIH (1986) provides TLV values for fumes, soluble salts and alkyl compounds of aluminum, since the TLVs are not based on extensive human data and inhalation toxicity data on these forms of aluminum are lacking, RfD_I values for these forms of aluminum cannot be derived.

Derivation of a CS for inhaled aluminum is complicated by the fact that specific information regarding pulmonary effect levels in humans is limited. It is apparent, however, that exposures exceeding the TLV by many times are necessary to elicit adverse effects. Fibrosis is an equivocal effect of aluminum exposure in humans and has not been produced in exposed animals. Lung alterations consistent with inhalation of nuisance particulates (potentially reversible effects), therefore, appear to be the most appropriate basis for a CS. Since these types of alterations have been produced in animals at known exposures, animal effect levels (see Section 3.2.2.) can be used to calculate the CS. Lung edema, pneumonia and pleurisy sufficient to induce death occurred in rats exposed to 33 g/m³ of aluminum oxide (~17.2 g aluminum/m³), 5 hours/day for up to 285/402 days (Klosterkotter, 1960). Slight increases in alveolar macrophages and some nasal irritation were observed in rats exposed to 2.18 mg/m³ of aluminum fibers, 5 days/week for up to 86 weeks (Pigott et al., 1981), but these effects seem minimally adverse. The 17.2 g aluminum/m³ FEL is equivalent to 1.6 g/kg/day if it is assumed that the respiratory rate was 0.223 m³/day and body weight was 0.35 kg. Multiplying this dose by the cube root of the ratio of animal weight to human body weight (assumed 70 kg) gives a human MED of 19.2 g/day for a 70 kg man. The RV_d associated with the dose is 1 since log MED is >3. The mortality associated with this exposure is given an RV_e of 10. A CS of 10, the product of the RV_d and RV_e, results. Since the CS associated with inhalation exposure to aluminum is greater than that associated with oral exposure, the inhalation CS of 10 is adopted to represent the toxicity of aluminum. A CS of 10 corresonds to an RQ of 1000.

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